FORMULATION AND DEVELOPMENT OF TIOPRONIN DELAYED RELEASE TABLET

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ABSTRACT

The goal of this research is to formulate and characterize a delayed release oral dosage form of Tiopronin. The delayed release tablet is intended to release the drug after some delay or after tablet pass GI tract. The enteric coating is common example of this tablet. All enteric coated tablets are delayed release tablet but all delayed release tablet are not enteric coated tablets. The present work aims to avoid degradation of drug in acidic environment of stomach. So due to enteric coating drug releases in to the small intestine so that drug gets larger surface area for absorption. The tablets were prepared by wet granulation method rather than direct compression because of cohesive property of the drug. Optimized core tablet then subjected for enteric coating by selected base coat polymer cellulose derivative for preventing core tablet from moisture. Dissolution results of tablets with enteric coating have shown release of Tiopronin in simulated gastrointestinal fluid pH 0.1N HCl, but most of the drug released in pH 6.8 Phosphate buffer. At the end it was found that prepared formulation gave satisfactory results compared with marketed sample dissolution profile. Hence prepared formulation by-pass the degradation of Tiopronin by enteric coating approach and can be used as single unit dosage for the treatment of acid-related diseases. Thus, a pharmaceutically equivalent, robust formulation of Tiopronin delayed release tablet was developed.

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INTRODUCTION-

Cystinuria, an inherited autosomal recessive disorder that can result in cystine stones forming in the kidneys, ureters, and bladder, is characterised by high amounts of the amino acid cystine in the urine as a symptom. An illustration of aminoaciduria. This disease is associated with the word "cystine," not "cysteine," as the latter is a dimer of the former.
Less than 50,000 people in the US are affected by this sickness. One in 10,000 people have cystinuria, according to statistics.

Cystinuria results in recurrent kidney stones. A disorder involving the abnormal transepithelial transfer of cystine and dibasic amino acids in the kidney and gut is one of the many causes of kidney stones. If the condition is not properly managed, the disease may cause significant damage to the kidneys and adjacent organs, as well as in rare instances, death. The stones may be identified if the test for nitroprusside cyanide is positive. The crystals are typically

hexagonal, white, and transparent. When first removed, the stones may be pink or yellow, but as they are exposed to the air, they ultimately turn greenish. If no stones form, cystinuria normally has no symptoms.
Patients with cystinuria need ongoing care since they pass stones every month, week, or day. Nonsteroidal anti-inflammatory drugs (NSAIDs) or over-the-counter (OTC) treatments should be taken with caution because kidney damage or poor function are usually present in cystinurics. Cystinurics are more likely to have chronic kidney disease.

Cystine stones are frequently missed by straightforward x-rays. Ultrasonography or computed tomography may be used in place of x-rays.

The aim of this research paper is to formulate, evaluate, and charatcerize a delayed-release tablet dosage form. The paper will present a detailed review of the literature on nephrolithiasis and the various treatment options available, as well as an overview of delayed-release tablet dosage forms and their advantages in treating cystinuria. The formulation of the delayed-release tablet dosage form will be based on an extensive literature review of active pharmaceutical ingredients (APIs) and excipients that have been shown to be effective in treating cystinuria. The formulation will be evaluated for its physicochemical properties, such as particle size, flowability, and dissolution rate.

The results of this research paper will provide valuable insights into the development of an delayed-release tablet dosage form for the treatment of cystinuria. This could potentially lead to the development of a more effective and patient-friendly treatment option for individuals suffering from cystinuria.

Materials and Method-

Materials-

Tiopronin as a gift sample from Sun Pharma Laboratories in Gurgaon. Eudragit, HPMC, talc, triethylcitrate, acetone are the excipients used in this study which were used as an analytical grade.

Method-

Identification of active pharmaceutical ingredient using IR Spectroscopy method-

The FT-IR spectrophotometer was used to develop the FT-IR spectrum. The infrared spectrum was taken for the pure drugs i.e. –Tiopronin. FTIR were carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy (FTIR). The drug-KBr ratio was taken, and the mixture was subjected to 10 tonnes of pressure in a hydraulic press in order to create a pellet. The produced pellet was placed within samples and kept there while the devices recorded the IR peaks. The acquired IR spectra was contrasted with the FT-IR spectrophotometer was used to develop the FT-IR spectrum. The infrared spectrum was taken for the pure drugs, i.e., Tiopronin. FTIR were carried out by the KBr disk method using computer mediated Fourier transform infrared spectroscopy (FTIR). typical IR drug spectrum. The produced pellet was placed within samples and kept there while the devices recorded the IR peaks. The acquired IR spectra has been contrasted with the typical IR drug spectrum.

Study of physicochemical properties of both Active Pharmaceutical Ingredients-

Pre-formulation studies-

Pre-formulation is a body of research that examines a novel drug candidate's physicochemical property and how they could affect dosage form development and drug performance. This might be useful for creating new products or demonstrating the necessity of molecular change. Before developing a pharmaceutical formulation, consideration must be given to the inherent chemical and physical characteristics of each medicine. This characteristic lays the groundwork for producing dosage forms by combining drugs with medicinal components.

Appearance: The evaluation of physical appearance is one of the most important drug tests. The color may reveal signs of impurity or pollution. The physical appearance of drug substances is tabulated in Table 1.

Melting point: A substance's melting point is often defined as the temperature at which it changes from a solid to a liquid. The temperature at which a liquid under atmospheric pressure changes from a solid to a liquid is known as its melting point. The melting point of a liquid at atmospheric pressure is the temperature at which it transforms from a solid to a liquid. At this point, the liquid and solid phases are in equilibrium. The melting points of drug compounds are determined by the melting point instrument. The melting point of both drug substances is mentioned in table 1.

Procedure (by Capillary tube method)-

The use of a capillary tube. A burner was used to screen the capillary tube, and after that, the capillary pipe was expanded with both ends grabbing it and pressing in opposing directions to screen it on one end. A little amount of telmisartan has been put on a sterile surface. The capillary tube has been filled with the substance. On the melting point unit, a capillary tube (Veego/Macro Scientific Works) is placed. As the sample started to melt, its temperature was continuously monitored and calculated using a thermometer. For the most trustworthy outcomes, gradual heating was adopted. It was noted that the sample begins to fuse and eventually completes the fusion.

Solubility studies: A small quantity of the drug sample was taken in a test tube, and the solubility was determined by dissolving the drug in 1 ml of various solvents. The solubility of both drug substances is mentioned in Table 1.

Particle size: PSD and shape have an impact on a drug's chemical and physical characteristics. It is commonly accepted that poorly soluble drugs are more accessible when given as a finely divided powder as opposed to a coarse substance during the rate-limiting phase of the absorption process. The flow, the size of the powder and granules, and the efficiency of their mixing are all impacted by the tablet's shape and size. The Malvern method is used to calculate the drug's particle size distribution (PSD). The details of particle size distribution for both drug substances are described in Table 2.

Bulk density and Tapped density: For measuring the bulk density and tapped density, a few grammes of powder are added to a 100 ml measuring cylinder and lightly agitated to dislodge any agglomerates that may have developed. The bulk density is then calculated. Following the initial volume measurement, the cylinder was set to fall independently onto a hard surface from a height of 2.5 cm every 2 seconds until no more volume changes were observed, at which point the tapping was stopped. The following formulas were used to determine BD and TD:

BD = weight of the powder / volume of the packing

TD = weight of the powder / tapped volume of the packing.

Hygroscopicity: As a function of humidity, a material's hygroscopicity (ability to absorb or release water) is measured (i.e., water activity) A moisture sorption isotherm that plots the changing water content against temperature and RH would be the best technique to measure hygroscopicity. The details of APIs hygroscopicity is mentioned in Table 3.

Drug-Excipient compatibility studies: Drug excipient compatibility was performed for physical observation and chemical evaluation for impurities through analysis (with a single API) stored at 228C/75% RH in open glass vials for four weeks. The excipient compatibility studies assessed common excipients acting as fillers, disintegrants, and glidants. The binary mixture-physical observation investigation on drug excipient compatibility is summarized in Table 4.

Characterization of formulation-

Drug substance particle size selection for product development-

The larger particle size of the pharmaceutical ingredient improves flow and increases its manufacturing potential. The physical and flow characteristics of drug substance were assessed, and the results are described. However, for those highly soluble medications, the particle size has little impact on in vivo performance.

The impact of drug product particle size on the homogeneity of content parameter is summarized in Table 5.

Sieve selection and sifting of API-

The first phase in the direct blending and mixing production process, which might affect the capsule assay and content uniformity, is the proper sieve selection.

Manufacturing process selection-

Manufacturing techniques such as direct mixing and blending were chosen. The aforementioned technique was used to prepare batches, and the resulting information was collated. Two methods of batch preparation, namely direct mixing and blending and direct mixing and blending with milling, were used to optimise the milling process.

Milling can be defined as the process in which we use a milling machine with rotatory cutters. It involves the application of the physical and mechanical breakdown of coarser particles into fine particles.

Procedure involved-

A solid pharmaceutical composition is provided that includes a core, an inner coating, and an outer coating. The core includes tiopronin as an active agent. Further, the inner coating, which includes a cellulose-based polymer, surrounds the core, and the outer coating, which includes an enteric polymer, surrounds the inner coating. All the ingredients were weighed. Lactose monohydrate, Hyydroxypropyl cellulose (low substitute) LH-11 and Hydroxypropyl cellulose (SL) were sifted using #25 ASTM mesh. Now, along with Tiopronin (API) were sifted using #25 ASTM mesh. Material was taken blended in polybag for 2 minutes. Now the material is taken for granulation. Unloaded mass were passed through Quadr co-mill through screen. Then, the material were dried in fluidized bed dryer. Weight of dried granules obtained. Dried

granules was sifted using #25 ASTM sieve. Retained material was then passed through Quadro co-mill through screen 40G. collected material was then passed through #25 ASTM sieve. Material was passed manually through #25ASTM sieve. Intra-granular and Extra-granular material weighed. Hydroxypropyl cellulose (LH-11) was sifted through #25ASTM sieve. Material along with weighed intra-granular portion was blended in 3.5L blender at 20 rpm for 20 minutes. Magnesium stearate was sifted using #60 ASTM sieve. Material was blended in 3.5 L blender at 20 rpm for 7 minutes. Lubricated blend was unloaded into polybag.

- **Procedure of preparing sub-coating dispersion:**

  All ingredients were weighed. Triethyl Citrate was added into Dichloromethane and Ethanol mixture. HPMC E-5 was added into mixture under continuous stirring till dissolved. Talc was added into the mixture and stirred continuously for 30 minutes. Quantity of the mixture has been given in table 6.

- **Procedure for preparing Enteric coating on Sub-coated tablet**

  All ingredients were weighed. Triethyl Citrate was added in Acetone and water mixture and this solution is divided into two parts. In part A, Eudragit L100-55 was added into the mixture under continuous stirring for 30 minutes. In part B, Talc was added into the mixture and homogenized for 15 minutes. Both part was added under continuous stirring. Dispersion was kept under stirring for 45 minutes. Prepared coating dispersion was taken for coating with following parameters. Dried tablets were placed in a polybag and sealed in a TLP with oxygen absorber. Quantities of the mixture has been discussed in table 7,8. The coating parameters were discussed in table 9,10. Tablet coating defects are examined and discussed in table 11.

In-vitro studies-

The dissolving was conducted for the innovator as well as for a variety of experimental studies. The findings are displayed below in a variety of ways. For the dissolution study, 900 ml of water has been used as dissolution media in USP-I (Basket type) apparatus at 100 rpm till complete dissolution of finished product took place. The solubility data of the finished product for trials 3 and 4 is described in table 12.

Result and Discussion-

Identification of active pharmaceutical ingredients using FTIR spectroscopy method-

FTIR spectroscopy is used for the identification of both APIs, which are available in pure form. Figures 1 contain the FTIR spectra of Tiopronin, respectively.

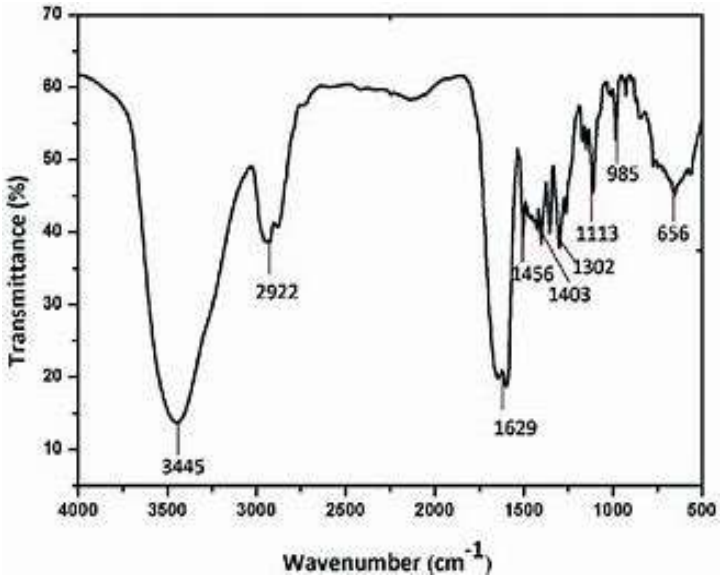

Figure 1. FTIR spectra of Tiopronin

Pre-formulation studies-

Appearance- The drug is white to off-white crystalline powder.

Melting point- The melting point apparatus is used to calculate the melting points of drug, and the results are provided in tabular form in Table 1.

Solubility studies- The solubility of the drug substances has been studied in various organic and inorganic solvents. The results of solubility are described below in Table 1.

Table 1. Melting point of drug substances

Sr. No.	DRUG	PHYSICAL APPEARANCE	MELTING POINT	SOLUBILITY
1	Tiopronin	White crystalline powder.	Approx. 93 to 98 °C	soluble in water, ethanol

Particle size distribution:

Table 2. PSD details of drug substances-

Particle size distribution	Tiopronin
D10	3.51 µ
D50	13.4 µ
D90	42.4 µ

Density: The density of Tiopronin was found to be 163.19 g·mol−1 respectively.

Hygroscopicity: In order to assess the hygroscopic nature of API, it provides a measurement of the sample's capacity to absorb and release water when both the APIs are exposed to the environment. The hygroscopicity of both the drug is mentioned in Table 3.

Table 3. Hygroscopicity of Drug substance-

Sr. No.	Drug	Result of The Determination
1	Drug	Non-Hygroscopic

Drug-excipient compatibility studies-

Based on the physical observation data of mixtures with individual of APIs, we can conclude that the selected excipients can be used in the formulation because no compatibility issue was observed with studied excipients. The results of compatibility studies were mentioned below in Table 4.

Table 4. Drug excipient compatibility study, binary mixture- physical observation

Trial No. Trial 1A			
API	**Ratio**	**Initial**	**Open, 40 ˚C/75% RH (1 M)**
API	NA	Off-white granular powder	No change in color, with free following powder

Table 4. Drug excipient compatibility study

S.No.	Drug: Excipient	Ratio
1	API	1:1
2	API: Lactose monohydrate (Supertab11SD)	1:1
3	API: Hydroxypropyl cellulose (Low substitute LH-21)	1:1
4	API: Hydroxypropyl cellulose (Low substitute LH-11)	1:1
5	API: Hydroxypropyl cellulose (Klucel ELF)	1:1
6	API: Hydroxypropyl cellulose (Nisso HPC- SL)	1:1
7	API: Magnesium Stearate	1:1
8	API: Magnesium Stearate	62:5:1
9	API: Magnesium Stearate	20:83:1
10	API: Triethyl citrate	1:1
11	API: Hydroxypropylmethyl cellulose (E5)	1:1
12	API: Talc	1:1
13	API: Methacrylic acid: ethyl acrylate copolymer (Eudragit L100 55)	1:1
14	API: Ethanol	1:0.1
15	API: Isopropyl alcohol	1:0.1

16	API: Dichloromethane	1:0.1
17	API: Purified water	1:0.1
18	API: Colloidal silicon dioxide	1:1
19	API: Microcrytalline Cellulose (ceolus KG1000)	1:1
20	API: Acetone	1:01

Drug substance particle size selection for product development-

Table 5. Proposed PSD limits for drug substances-

S. No.	**API**	**PSD details**		
		D90 (µ)	**D50 (µ)**	**D10 (µ)**
1	API A	NMT 80 µ	NMT 30 µ	NMT 10 µ

Table 6: SUBCOATING ON TABLETS

Ingredients	**100mg/tab 5%(w/w)**	**%w/w solids (for coating dispersion only)**	**Quantity to be taken (g)**	**Actual quantity taken (g)**
Drug	170.000	-	-	-
HPMC E-5	5.100	60	35.700	35.70
Triethyl citrate	0.510	6	3.570	3.57
Talc	2.890	34	20.230	20.23
Dichloromethane (DMC)	q.s.	-	395.250	395.25
Ethanol	q.s.	-	395.250	395.25

Table 7: Enteric coating on sub coated tablets

Ingredients	Mg/tab (5%)	%w/w solids (for coating dispersion only)	Quantity to be taken (g)	Actual quantity taken (g)
Drug	178.500	-	-	-
Eudragit L 10055	4.463	50.00	31.241	31.24
Triethyl citrate	0.446	5.00	3.122	3.12
Talc	4.016	45.00	28.112	28.11
Acetone	q.s.	-	747.023	747.02
Water	q.s.	-	83.003	83.00

Table8: Additional coating over enteric coated tablet

Ingredients	**Mg/tab**	**%w/w solids (for coating dispersion only)**	**Quantity to be taken (g)**	**Actual quantity taken (g)**

Drug	187.015	-	-	-
Eudragit L 10055	1.216	50.0	8.509	8..51
Triethyl citrate	0.121	5.00	0.850	0.85
Talc	1.094	45.00	7.657	7.66
Acetone	q.s.	-	203.475	203.48
Water	q.s.	-	22.608	22.61

Table 9: Prewarm coating parameters

Parameter	Temperature
Actual temperature (℃)	56
Exhaust temperature (℃)	33
Bed temperature (℃)	32
Pre warm temperature (℃)	50
Pan rpm	3

Table 10: Coating parameters

S.no.	Parameters	Initial	15 min	30 min	45 min
1	Inlet temperature	45	40.0	45.0	45.0
2	Exhaust temperature	40	40	40	40
3	Pan rpm	10.1	10.1	10.1	10.1
4	Spray pump speed	06.21	06.25	08.35	09.85

Table 11: Tablet coating defects

S.no.	Defects	Tested
1	Tablet picking	Visually inspected
2	Peeling and roughness	Visually inspected
3	Tablet edge chipping/ erosion	Visually inspected
4	Bridging and filling of logos	Visually inspected
5	Cracking of film coatings	Visually inspected
6	Surface irregularity	Visually inspected
7	Colour variability	Visually inspected

In-Vitro dissolution study

In pH 0.1, 6.8, the in vitro release capability of API was evaluated. In accordance with SOP, samples were collected for the dissolution analysis at 2hr in pH 0.1N HCl and 15, 30,45,60 minutes in pH6.8. Filtrates from SOP were used to calculate the cumulative release amounts at each time point and to further understand the release curve. The parameters of the dissolution research are presented in table 12.

Table 12: Dissolution conditions for API

Dissolution parameters	API	API
Medium	pH 6.80 phosphate buffer	pH 0.1N HCl
Apparatus	USP Type I	USP Type I
Volume	900 ml	900 ml
Agitation	100 rpm	100 rpm
Measuring time	60 minutes	120 minutes
Temperature	37°C±0.5°C	37°C±0.5°C
Volume withdrawn	10 ml	10 ml
Volume correction	Yes	Yes

Table 13: % Release (API) in acid stage

S.No.	2 hr
1	1
2	1
3	1
4	1
5	1
6	2
Mean	1
% RSD	40.0
Min	1
Max	2

Table 14: % Release (API) in buffer stage

S.No.	5 min	10 min	15 min	20 min	30 min	45 min	60 min	Inf
1	1	2	3	8	28	65	91	101
2	2	2	5	14	36	72	95	101
3	1	2	3	10	36	72	93	97
4	1	2	3	7	41	83	99	102
5	1	2	3	8	38	71	89	97
6	3	4	8	20	48	81	97	99
Mean	2	2	4	11	38	74	94	100
% RSD	40	40	50	45.5	17.4	9.2	3.9	2.2
Min	1	2	3	7	28	65	89	97
Max	3	4	8	20	48	83	99	102

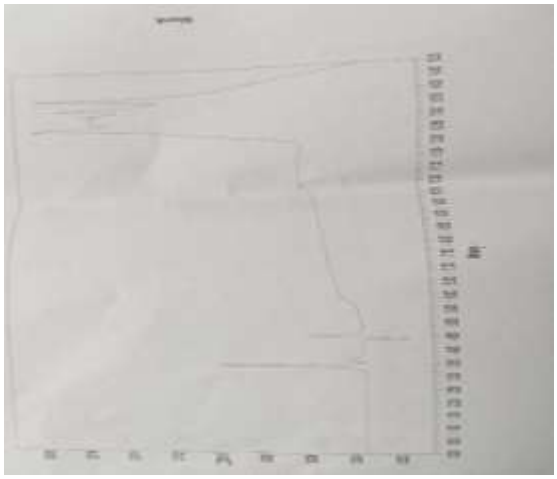

Figure 1: Acid stage blank

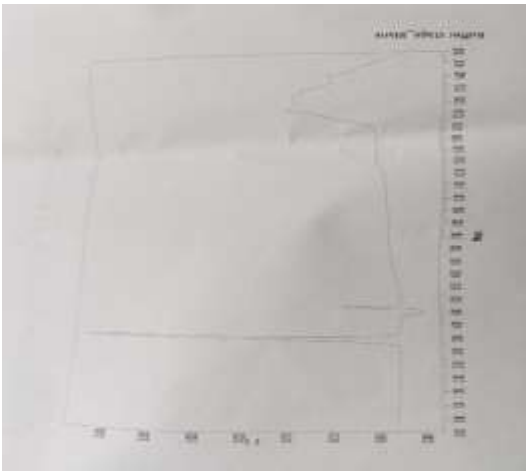

Figure 2: Buffer stage blank

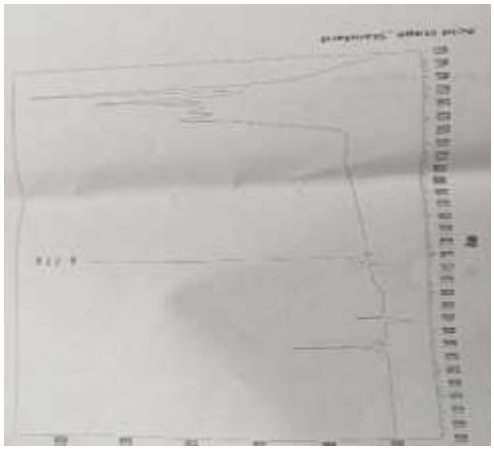

Figure 3: Acid stage standard

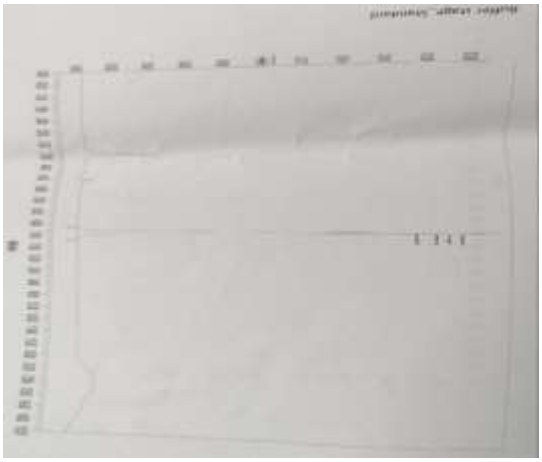

Figure 4: Buffer stage standard

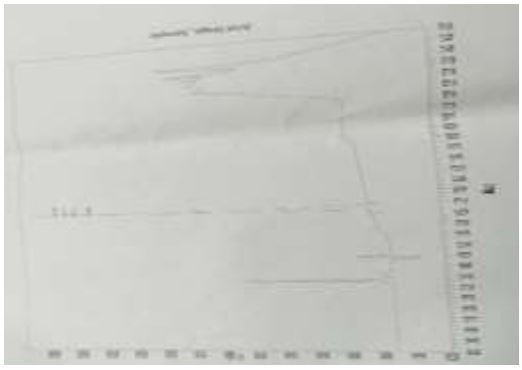

Figure 5: Acid stage sample

Figure 6: Buffer Stage Sample

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